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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/746,921	12/22/2000	Kevin J. Thorne	2265-15	2764

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EXAMINER
PATTEN, PATRICIA A

ART UNIT	PAPER NUMBER
1651	12

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/746,921	Thorne et al.
Examiner	**Art Unit**
Patricia Patten	1651

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Apr 30, 2002*.

2a) ☐ This action is **FINAL.** 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-23* is/are pending in the application.

4a) Of the above, claim(s) *9 and 11-23* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *1-8 and 10* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) X Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s).
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s).	6) ☐ Other.

DETAILED ACTION

Election/Restriction

Applicant's election of Group I, Claims 1-10 and the election of a bone growth composition species in Paper No. 2 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 11-23 have been withdrawn from further consideration on the merits as being drawn to a non-elected invention. Further, claim 9, drawn to the non-elected species, has been withdrawn from consideration as being drawn to a non-elected invention.

Applicants were uncertain of the shortened period for response. Applicants were given an extension of one month to furnish a response to the non-responsive letter sent 2/14/02 (as indicated in the Interview Summary which took place on 4/1/02). Thus, a response was necessary before 3/14/02 in order to avoid a fee for an extension of time. Because the most recent response was filed 4/30/02, a two month extension fee was charged.

Claims 1-8 and 10 have been presented for examination on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1- 8 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1- 8 and 10 either recite, or depend upon a claim which recites 'acidic buffering potential.' This phrase is indefinite in that the meaning of the phrase is not well understood. The term could mean that the composition tends to offer an acidic potential to the environment, or alternatively, that the composition buffers an acidic environment (i.e., making the environment more basic). The phrase 'acidic buffering potential' is not found in the art, and thus, the Examiner cannot determine the specific meaning of the phrase. Limitations from the Specifications are not read into the claims. Additionally, the term 'potential' itself is indefinite in that it does not define the composition fully. *Does* it provide for 'acidic buffering' or not? The manner in which the phrase reads only recites a 'potential' to provide 'acidic buffering.' Although the claims are deemed indefinite because said phrase is not clearly delineated, the Examiner will examine the claims as though the composition offers at least some hydrogen ions to the surrounding environment.

Claims 1- 8 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a substrate, a bone growth protein, a source of calcium and a source of phosphate, does not reasonably provide enablement for a composition which has an 'acidic buffering potential' in physiological solution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. Claims drawn to pharmaceutically acceptable compositions and to methods of administering compounds to humans generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments.

In the Instant case, Applicants have speculated that the composition of the present invention will increase the acidity of the physiological area around the composition due to the acidic nature of the calcium phosphate compounds. Although Applicants have contended that the bone matter compositions were derived from the more acidic calcium phosphate compounds such as calcium monophosphate, and calcium pyrophosphate for example, it has not been shown in the Instant specification wherein the composition of the Instant claims actually decreases physiological pH. Although the composition may itself be acidic, will the composition degrade at such a rate to release hydrogen ions rapidly enough to actually lower the pH of the physiological medium? This concept has not been found in the art, nor has it been substantiated in the Instant specification.

It is known in the art that the more acidic forms of calcium phosphate are combined to make matrices such as brushite and monetite (a 1:1 ratio of calcium and phosphate). Applicants' only working example was carried out using Ostite. Ostite, as disclosed by Applicants is sold by Millennium Biologix in Kingston, Canada (p.18, Instant specification). However, it is not known exactly what Ostite is made of, nor how it is made. If this substance is different than the well known brushite and monetite matrices known in the art, the difference has not been described in the Instant specification. *The art of creating artificial biocompatible bone material is unpredictable*. Slightest variations in the type of calcium compounds may dramatically change the overall physical characteristics of the 'bone material' (See for example, Constantz US 5,047,031 col.4, line 6 - col.5, line 2).

It is deemed that the Instant Specification has not provided the skilled artisan with enough information regarding the composition in order to reproduce a bone material which would actually degrade at such a rate which would consequently 'acidify' the physiological medium surrounding said material.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with

first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohura et al (1999). Claims 1-4, 8 and 10 are drawn to a composition comprising a substrate, a bone growth protein, a source of calcium, a source of phosphate, and wherein said composition has an 'acidic buffering potential.' Claims are further drawn to wherein

the source of calcium is an acidic calcium phosphate salt such as calcium monophosphate, wherein the bone growth protein is selected from purified bone growth factors and recombinantly produced bone growth factors, and wherein the bone growth protein comprises Bone Protein.

Ohura et al. (1999) taught a β-TCP-MCPM cement which was combined with rhBMP-2 for healing bone (Abstract). MCPM is monocalcium phosphate monohydrate, an acidic form of calcium phosphate. Thus, the composition provided for a 'source of' calcium and phosphate wherein the calcium monophosphate would have had an 'acidic buffering potential.' The cement itself was molded into the 'substrate' matrix for the BMP as described on p. 169.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwan et al. (US 6,187,047 B1) in view of Constantz (US 5,047,031). The nature of claims 1-5

and 8 were discussed *supra*. Claims 6-7 are additionally drawn to wherein the source of phosphate is a sodium phosphate salt and wherein the substrate is selected from collagen, fibrin and alginate.

Kwan et al. (US 6,187,047 B1) described artificial bone matrices which included collagen as a substrate, on which calcium phosphate 'cements' were added (col.3, lines 15-58). Kwan et al. Further taught that proteins such as BMP's and TGF-β were advantageously added to the composition. Kwan et al. did not specifically teach the use of acidic forms of calcium phosphate compositions.

Constantz (US 5,047,031) taught that the acidic forms of calcium phosphate compositions were well known in the art to be suitable matrices for bone growth/repair (col.4, lines 56-64).

One of ordinary skill in the art would have had expected that the 1:1 ratio of calcium to phosphate added onto a collagen matrix would have been a suitable choice for the production of a bone matrix since Kwan et al. Taught that collagen was a stable support for the calcium phosphate cement, and since Constantz taught that brushite and monetite were suitable bone cements.

Although neither reference specifically stated wherein the calcium phosphate was calcium monophosphate for example or wherein the source of phosphate was a sodium phosphate salt, one of ordinary skill in the art would have recognized that these salts would have provided for a matrices which was a 1:1 ratio of calcium to phosphate (i.e., brushite

or monetite). Thus, the addition of any salts which would have created the 1:1 combination would have been obvious to one of ordinary skill in the art. The choice of salt (calcium or sodium phosphate) would have therefore merely been a matter of judicious selection, since each would have acted as functional equivalents.

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohura et al (1999) in view of Kwan et al. (US 6,187,047 B1). The nature of the claims, as well as the teachings of Ohura et al. and Kwan et al. were discussed *supra*.

Ohrua et al. taught the creation of a bone matrix via use of calcium monophosphate however, did not teach the use of a collagen substrate.

Kwan et al. taught that collagen was a suitable substrate for calcium phosphate cements.

One of ordinary skill in the art would have been motivated to have combined the cement proposed by Ohura et al. which contained calcium monophosphate as an ingredient onto a substrate such as collagen in order to afford the composition additional support *in-vivo* leading to increased bone formation.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the

art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Patricia Patten, whose telephone number is (703)308-1189. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon P. Weber, Ph.D
Primary Examiner